

HORMONE RESEARCH

From Developmental Endocrinology to Clinical Research



ABSTRACTS

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growth ($p > 0.2$).

Conclusions: Our data link the GHRd3 variant to both catch-up growth and parameters of glucose homeostasis in ELBW infants. Whereas the impact of IGF-1 -575 G/A on glucose homeostasis seems to be only moderate in preterm infants, those carrying GHRd3 may bear an increased risk for the development of insulin resistance in adulthood.

PO2-128 Genetics of Growth II

Holoprosencephaly associated gene mutations as a possible cause of pituitary stalk interruption syndrome (PSIS)

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Background: Holoprosencephaly (HPE) is characterized by great phenotypic variability. The phenotypic spectrum ranges from minor defects like hypotelorism or single central incisor (SCI) to severe malformations. Potential pathogenetic mechanisms include genetic and environmental factors. Mutations in genes located in various chromosomal loci have been associated with HPE, Sonic Hedgehog (SHH), TGIF, SIX3 and ZIC2 being the most extensively studied. PSIS syndrome constitutes a distinct midline defect of unknown pathogenetic mechanism. It seems however that genetic, as well as, environmental factors are implicated. Based on the observation that 3 of our patients with PSIS also had SCI, a characteristic found in certain HPE cases, we initiated a search for mutations in HPE associated genes.

Patients and methods: Thus far mutations in the TGIF and SHH genes have been looked for in 30 patients with MPPH associated with PSIS and ectopic neurohypophysis.

DNA was extracted from peripheral lymphocytes and the entire coding regions of TGIF gene (exons 2 to 4) and of the SHH gene (exons 1 and 2) were PCR amplified and sequenced. PCR amplification and sequencing of SHH exon 3 was unsuccessful due to its high GC content.

Results: One of our patients was found to carry a novel heterozygous C to T nucleotide transition at position 799 of the TGIF gene. This molecular defect results in a premature stop codon at Q267X in the repression domain 2b of exon 4 of the TGIF gene. This mutation results in a truncated protein (5 amino acid shorter than the wild type peptide).

A second patient had an 18p deletion. The deleted part included the TGIF gene. Thus far no mutation has been detected in exons 1 and 2 of the SHH gene in our patients with PSIS.

Conclusions: Our data suggests that in certain cases of PSIS, mutations of the HPE genes may be implicated.

PO2-129 Genetics of Growth II

Presence of the exon 3 deleted isoform of GH receptor (GHRd3) does not influenced on clinical and laboratory characteristics, IGF-1 generation test and the response to rGH treatment in children with ISS

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Introduction. GHRd3 polymorphism has been reported to be associated with responsiveness to rGH therapy in children with variety range of growth disorders (GH deficiency, SGA, ISS and Turner syndrome) in some but not in all studies. Recently was reported that children with ISS carrying the GHR d3 allele present a higher GH sensitivity on IGF-1 generation than children homozygous for GHR fl allele. On other hand, this correlation did not observed in children with GH deficiency.

Aim. The aim of our study was to evaluate the influence of the GHRd3 polymorphism on clinical data and laboratory parameters (including IGF-1 generation test) and responsiveness to rGH treatment in children with ISS.

Materials and methods. The study included 39 prepubertal children with ISS (31 boys and 8 girls). Standard GH stimulation test (clonidin) and IGF-1 generation test (rGH 33 mk/kg/day during 4 days) were performed in all children. The GHRd3 polymorphism was genotyped by PCR assay. Patients received rGH therapy at dose 40.8 ± 10.3 mk/kg/day with duration of treatment from 6 up to 12 months.

Results. The distribution of GHR genotype (56.4% - fl/fl, 41% - fl/d3 and 2.6% - d3/d3) was similar previously reported in 150 healthy (control) group in Russian population (Orlovski, 2004). Basal clinical data and laboratory findings in children with different genotypes were similar. Interestingly, that basal GH concentration was a statistically significant higher in children with GHR d3 allele than in children homozygous for GHR fl allele (1.18 ± 1.20 for fl/fl vs. 0.74 ± 1.03 for fl/d3 and d3/d3; $P = 0.037$). No statistically significant differences in changes of IGF-1 concentration were found in both groups neither at short-term generation test nor during 6-12 months of rGH treatment. Growth effect of treatment (height velocity, changes in height SDS) did not differ statistically among genotypes.

Conclusions. Analysis for GHRd3 polymorphism in children with ISS does not give sensitive predictions of phenotype and cannot predict growth response to rGH treatment.

PO2-130 Genetics of Growth II

Genotype-phenotype correlation in children with SHOX gene variants

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Background Haploinsufficiency of *Short stature Homeobox-containing gene* (*SHOX*) is known to cause short stature. Multiple mutations as well as allelic variants (Vs) have been described, but the clinical significance of Vs is not known.

Objectives To define the clinical and biochemical correlates of *SHOX* Vs in patients with short stature.

Methods We retrospectively reviewed records of patients (pts) referred for short stature over 6 years, with *SHOX* tested as part of clinical care at Esoterix Labs (CA). Pts with chromosomal or skeletal abnormalities (i.e. Turner Syndrome, Leri-Weill dyschondrosteosis) were excluded. *SHOX* Vs included partial gene deletions, mutations previously described as allelic variants, and previously undescribed mutations. We compared Height (Ht) SDS; IGF-1 SDS; and Bone Age/Chronologic Age ratio (BA/CA) between pts with *SHOX* Vs and normal *SHOX*. Growth Hormone (GH) stimulation tests were done using Arginine & L-Dopa, normal GH ≥ 10 ng/mL. Among GH treated pts, Ht SDS, IGF-1 SDS, Growth velocity (GV) and GH dose were compared at baseline, 6, 12 and 24 months. Hypothesis test of equal means and Fisher's exact test (SAS) were used for comparison.

Results Among 335 pts tested for *SHOX* mutation, 17 were excluded (12 chromosomal, 5 skeletal abnormalities, of whom 7 had whole *SHOX* gene deletions). Among 318 included pts, 83 had *SHOX* Vs (S+), with 19 different *SHOX* mutations. Nucleotide change c.277+17G>T was found in 43% of S+ group. There were no differences at baseline in age, Ht SDS, and BA/CA between S+ and pts with normal *SHOX* (S-).

Table 1. Baseline Comparison

Variable	S+ Mean (SD) n=83	S- Mean (SD) n=235	p
Age (yr)	9.78 (3.68)	10.61 (3.47)	0.06
Ht SDS	-1.96 (0.70)	-2.06 (0.75)	0.31
IGF-1 SDS	-1.46 (1.21)	-1.84 (1.36)	0.19
BA/CA	0.85 (0.11)	0.86 (0.11)	0.60

GH stimulation tests were performed in 57% of pts; there was no difference in % of GH deficient pts (S+ 42.6%, S- 39.8%, $p=0.74$). Among 38% of pts treated with GH, Ht SDS, IGF-1 SDS, GV and GH dose did not differ significantly at baseline, 6, 12 and 24 months (S+ n=31, 30, 24, 16; S- n= 91, 76, 66, 42, respectively). Subgroup analysis comparing c.277+17G>T and S- groups